Resume of the proposed research topic on:

"Advanced Machine Learning Algorithms for Digital Histopathological Image Analysis"

by

Prasad Vilas Dutande

Research Scholar

Under the guidance of

Dr. Suhas Gajre
Professor

Department, Electronics & Telecommunication Engineering,

S.G.G.S. Institute of Engineering and Technology,

Vishnupuri, Nanded – 431 606, INDIA.

E-mail: ssgajre@sggs.ac.in, Phone No.: +91-9421851011

1. Introduction and Motivation:

Advance Machine Learning is the trendiest tool in a medical image processing toolbox. This exciting class of methods, based on artificial neural networks, quickly became popular due to its competitive performance in prediction problems. In pioneering early work, applying simple network architectures to abundant data already provided gains over traditional counterparts in medical image analysis, and medical diagnostics. Now, ideas for constructing and training networks and even off-the shelf models have been adapted from the rapidly developing machine learning subfield to improve performance in a range of medical image detection and diagnosis tasks. There are two main reasons why deep learning is appealing to medical domain fraternity. First, this powerful class of models can, in principle, approximate nearly any input to output mapping if provided enough data. Second, deep neural networks can learn directly from raw input data. Contrary to the traditional machine learning approaches, this obviates the need for laborious feature crafting and extraction and, in principle, allows using the networks as off-the-shelf black box tools. As large-scale medical imaging data are

available from publicly available cohorts, and methods for learning the thousands of network parameters have matured, the time is now ripe for taking advantage of these powerful models.

Over the past few decades, medical imaging techniques, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Mammography, Ultrasound, X-ray images have been used for the detection, diagnosis, and treatment of myriad diseases including cancer. Apart from these medical image modalities, one more modality that has grown up these days is Digital Pathology. Digital pathology has emerged with the digitization of patient tissue samples and in particular the use of digital whole slide images (WSIs). Whole slide Images (WSI) acquired with highly automated scanners have the potential of providing a valuable assistance to pathologist in his daily practice. The advent of digital pathology not only simplify storage and sharing of stained slides, but also paves the way for the automatic analysis of very large cohorts with image analysis and deep learning methods in order to quantitatively model these challenging and rich data.

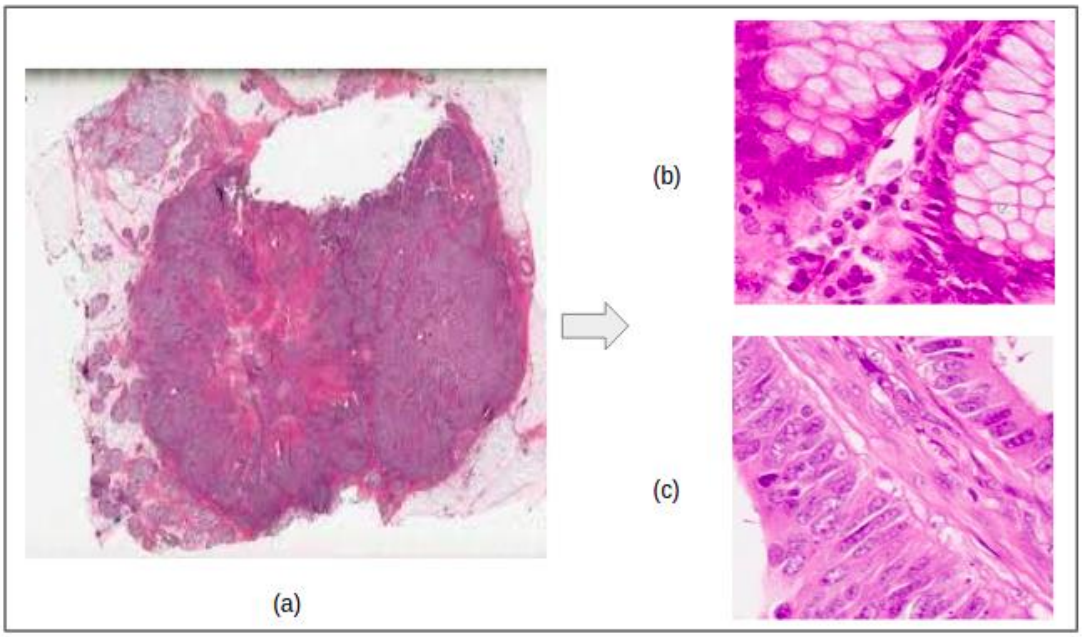

Figure 1. Example of Digital Pathology Whole Slide Image (WSI)

In histopathology, microscopic images of tissue samples are examined to study the manifestations of disease. Reagents that bind to specific proteins, called stains, are used to increase the contrast between different structures for their manual examination. By

far the most commonly used staining scheme is a combination of hematoxylin and eosin (H&E). Hematoxylin is a bluish-purple basophilic dye that binds strongly to the nuclei while eosin is a red-pink stain that binds primarily to acidophilic proteins in the cytoplasm and the stromal matrix. Figure 1 shows an example of WSI and samples of extracted patches from it. Due to inconsistency in staining and image acquisition, histopathological images suffer from color and illumination variations. The main factor that influences the color variation is the difference in staining procedures adopted in different laboratories. Figure 2 depicts variation of colors in histopathological images. In order to resolve this issue, various color normalization techniques are used such as structure preserving color normalization, nonlinear mapping approach, Blind color decomposition.

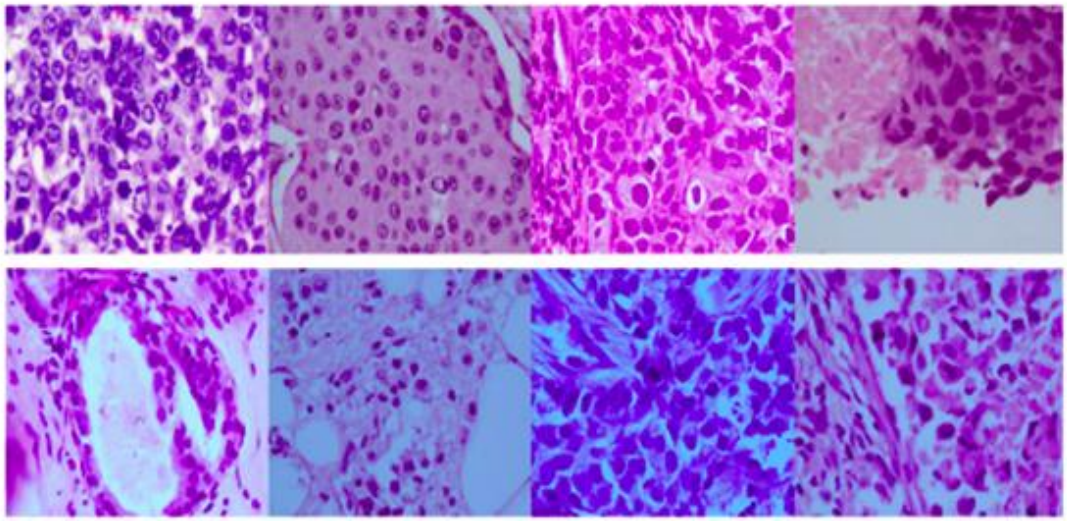

Figure 2. Sample images to demonstrate the color shade and illumination variations.

2. Related Literature Review:

Deep learning methods are highly effective when the number of available samples are large during a training stage. For example, in ImageNet Large Scale Visual Recognition Challenge (ILSVRC), more than 1 million annotated images were provided [1]. However, as for medical applications, we usually have a very limited number of images, *e.g.*, less than 1,000 images. Therefore, one of the main challenges in applying deep learning to medical images arises from the limited small number of available training samples to build deep models without suffering from overfitting. To this end, research groups have devised various strategies, such as (i) to take image patches either 2D or 3D as input [2][3][4], rather than the full-sized images, to reduce the input dimensionality, thus the number of model parameters; (ii) to expand their

dataset by artificially generating samples via affine transformation (*i.e.*, data augmentation) and then train their network from scratch with the augmented dataset [4]; (iii) to use deep models trained over a huge number of natural images in computer vision as 'off-the-shelf' feature extractor and then train the final classifier or output layer with the target-task samples [5]; (iv) to initialize model parameters with those of pre-trained models from non-medical or natural images and then fine-tune the network parameters with the task-related samples [6][7]; (v) to use models trained with small-sized inputs for arbitrarily-sized inputs by transforming weights in the fully connected layers into convolutional kernels [3][8].

The computer vision community has gained momentum in medical image analysis. This is due to recent advances in a range of applications such as lesion detection and classification, semantic segmentation, registration and image enhancement with the development of deep learning algorithms, especially the convolutional neural network (CNN). This has led to the development of several approaches for the generation and translation of image data. The most prominent of those are GANs.

In 2014, I. Goodfellow introduced Generative Adversarial Networks (GANs). They are generative models with the objective of learning the underlying distribution of training data in order to generate new realistic data samples which are indistinguishable from the input dataset. Prior to the introduction of GANs, state-of-the-art generation models, such as Variational Autoencoders (VAE), tackled this task by performing explicit density estimation. GANs constitute an alternative to this by defining a high-level goal such as generate output data samples which are indistinguishable from input data and minimizing the loss function through a second adversarial network instead of explicitly defining it.

Gurcan et al. [9] summarized the recent state-of-the-art CAD technology for histopathological image analysis. The authors have also emphasized the usage of standard datasets for the evaluation of developed CAD systems since it helps in easier analysis and comparison. Various methods proposed for the analysis of BCHI discussed the complexity of the tissue characteristics that need to be studied to improve the robustness of the system.

Systematic study on assigning of an image color to another image was carried out by Reinhard exhibits color characteristics of a template image are brought to an input image based on mean and standard deviation in LAB color space representation.

This method is popularly known as the Rehinard method. To improve the color consistency in histopathological images an Expectation-Maximization (EM) based segmentation–driven Standardization (EMS) algorithm is used. In this approach, the input and the normalized image were qualitatively compared during the nuclei segmentation step. To obtain an accurate stain density map in histopathology images Vahadane et al. [10] proposed a Structure-Preserving Color Normalization (SPCN) algorithm. They converted the source and the target RGB images to optical density space using the Beer-Lambert law. The structure of the original image is preserved by employing the SPCN algorithm. But this method fails to preserve the color information of the source image and suffers from local minima.

A more vigorous review is carried out based on various tasks in histopathology image analysis.

A) Nuclear Instance Segmentation

Within the current literature, energy-based methods, in particular the watershed algorithm, have been widely utilized to segment nuclear instances. For example, researchers used thresholding to obtain the markers and the energy landscape as input for watershed to extract the nuclear instances. Nonetheless, thresholding relies on a consistent difference in intensity between the nuclei and background, which does not hold for more complex images and hence often produces unreliable results. One of the literatures have introduced a stain-aware multi-scale convolutional network, so-called SAMS-Net, for segmenting nuclei in WSIs. The architecture of SAMSNet was inspired by the fully convolutional network (FCN) architecture. In particular, SAMS-Net employs a set of pre-defined weight maps aware of the intensity of hematoxylin in each histopathological image. SAMS-Net extracts deep contextual features in the downsampling path and localizes nuclei in the up-sampling path. The performance of SAMS-Net was evaluated on the nuclei segmentation dataset achieving a Dice score of 81.2%. A deep interval-marker-aware network called DIMAN for nuclei segmentation. DIMAN combines the convolutional neural networks with the marker-controlled watershed. DIMAN has been trained to segment the foreground, marker, and interval of nuclei simultaneously. The performance of DIMAN was assessed on three public histopathology image datasets, achieving an aggregated Jaccard index (AJI) score of 56.64% with the MoNuSeg dataset. Existing automated nuclei cell segmentation methods still face several challenges when segmenting nuclei in WSIs, most

importantly the color variation in WSIs due to the use of different stains, as well as the intrinsic variation in cell types and sizes.

B) Nuclear Classification

As well as performing instance segmentation, it is desirable to determine the type of each nucleus to facilitate and improve downstream analysis. It is possible for current models to differentiate between certain nuclear types in H&E, however sub-typing of lymphocytes is an extremely hard task due to the high levels of similarity in morphological appearance between T and B lymphocytes. Typically, classifying each nucleus is done via a two-stage approach, where the first step involves either nuclear segmentation or nuclear detection. When segmentation is used as the initial step, a series of morphological and textural features are extracted from each instance, which are then used within a classifier to determine the nuclei classes. For example, researchers have classified nuclei within H&E stained breast cancer images as either tumor, lymphocyte or stromal based on their morphological features. Researchers performed nuclear segmentation and then classified each nucleus with AdaBoost classifier, utilizing the intensity, morphology, and texture of nuclei as features. For nucleus classification, usually a patch centered around a nucleus is input to a neural network, which makes detection or segmentation a prerequisite task. For example, SCCNN uses a novel neighboring ensemble predictor to label individual nuclei that follows detection by a spatially constrained convolutional neural network, while Hover-Net performs simultaneous nucleus segmentation and classification using horizontal and vertical distance maps to resolve and separate clustered nuclei. Recently, mask-RCNN has also been used for the joint segmentation and classification of various types on nuclei in H&E stained tissue images of lung adenocarcinoma.

C) Domain Adaptation

In recent years, there have been many studies on unsupervised domain adaptation for transferring the learned representative features from the source to the target domain. The works based on CNN show significant advantages due to better generalization across different distributions. With the development of the Generative Adversarial Networks (GAN), studies show the synthesized images could be used to perform unsupervised domain adaptation in a learned feature space where a generator is applied to learn the image distribution and generate the synthetic images while a discriminator

is trained to differentiate the synthesized and the real distribution. For example, Generate-to-Adapt proposes to learn a joint embedding space between the source and target domain, where the embedding space could be used to synthesize both the source and target images.

3. Methodology for Research:

Inspired by the work carried out in above literature, we would be learning the broader types of Machine Learning techniques and then focus on the Deep Learning framework to accomplish various pattern recognition tasks in medical image analysis. Machine Learning methods are broadly categorized as supervised or unsupervised based on the training data used to learn the computational models. Deep Learning based methods can fall in any of these categories.

A. Supervised Learning Models:

1. Convolutional Neural Networks (CNNs):

Currently, CNNs are the most researched machine learning algorithms in medical image analysis. The reason for this is that CNNs preserve spatial relationships when filtering input images. As mentioned, spatial relationships are of crucial importance in radiology, for example, in how the edge of a bone joins with muscle, or where normal lung tissue interfaces with cancerous tissue. A CNN takes an input image of raw pixels and transforms it via several Convolutional Layers with activation functions and Pooling Layers. This feeds into a final Fully Connected Layer which assigns class scores or probabilities, thus classifying the input into the class with the highest probability.

2. Transfer Learning with CNNs:

Unlike general natural image recognition tasks, medical image analysis lacks large labelled training datasets. Transfer learning involves training a machine learning algorithm on a partially related or unrelated dataset, as well as a labelled training dataset, to circumvent the obstacle of insufficient training data. Essentially the weights learned or pre-trained during the training of a CNN on one (partially related or un-related) dataset are transferred to a second CNN, which is then trained on labelled medical data using these weights. The weights can be applied to some or all layers of the CNN, except the last fully connected layer.

3. Recurrent Neural Networks (RNNs):

RNNs have been employed in text analysis tasks, like machine translation, speech recognition, language modelling, text prediction and image caption generation. In a plain RNN, the output of a layer is added to the next input, and this is fed back into the layer, resulting in a capacity for contextual 'memory'. To avoid vanishing gradient problems with backpropagation through time, plain RNNs have evolved into Long Short-Term Memory (LSTM) networks and Gated Recurrent Units (GRUs). In the medical image analysis space, RNNs have been used mainly in segmentation.

B. Unsupervised Learning Models:

1. Autoencoders:

Autoencoders learn feature representations of input data (called codings) in an unsupervised manner without labelled data. It is a model that takes input data, gleans codings from this, and then uses these codings to reconstruct output data (called reconstructions). The rationale behind autoencoders is that the output data must be as similar to the input data as possible, i.e., autoencoder models contain a cost function which penalizes the model when inputs and outputs are different.

2. Restricted Boltzmann Machines and Deep Belief Networks:

RBMs are generative, stochastic, probabilistic, bidirectional graphical models consisting of visible and hidden layers. These layers are connected to each other but there are no connections within the layers themselves. RBMs use the backward pass of input data to generate a reconstruction and estimate the probability distribution of the original input. RBMs can be efficiently trained with Contrast-Divergence algorithms and stacked into Deep Belief Networks (DBNs), where the hidden layer output of a RBM becomes the input for the visible layer of a second RBM stacked on it.

3. Generative Adversarial Networks (GANs):

GANs represent a type of unsupervised learning which holds promise for medical image analysis tasks. GANs comprise of two simultaneously trained, competing models, which may be multilayer perceptron such as CNNs. One CNN is a generator that generates artificial training images. The other CNN is called a discriminator, which classifies if images are real training images or artificial ones from the generator. The desired endpoint of this adversarial arrangement is one where the discriminator is

unable to tell the difference between a real and a generated image i.e., the probability of assigning an image to either data distribution is 1/2.

The noteworthy publicly available datasets with nuclear annotations in H & E stained slides are listed in Table 1. The MoNuSeg dataset for this challenge was obtained by carefully annotating tissue images of several patients with tumors of different organs and who were diagnosed at multiple hospitals. CoNSeP [20] was one of the first open-source datasets to provide the segmentation boundaries of nuclei along with their associated class labels, enabling the development of simultaneous nuclear segmentation and classification approaches. MoNuSAC [37] provides the segmentation mask and class labels for nuclei extracted from TCGA and sub-categorizes inflammatory cells as either lymphocyte, neutrophil, eosinophil, or macrophage.

Table 1. Datasets of annotated nuclei in H&E images.

Dataset	Nuclei	Label Type	Organs
MoNuSeg [12]	21,623	Instance	7
CRCHisto [13]	22,444	Detection + Classification	1
CoNSeP [14]	24,319	Instance + Classification	1
PanNuke [15]	205,343	Instance + Classification	19
MoNuSAC [16]	46,909	Instance + Classification	4

4. Proposed Research Work:

To develop computer algorithms based on advanced machine learning techniques for better visual interpretation of microscopic histopathology images of a disease by pathologists for the purpose of accurate diagnosis, to prepare precise treatment plan, and to review the post treatment response of the patients. Hence it is decided to pursue following objectives:

- To develop a novel supervised and unsupervised image translation algorithms for new synthetic data generation for histopathological image pattern recognition tasks.

- To design and develop unique deep learning architectures for applications in histopathological image analysis.
- To investigate unsupervised algorithms that can generate the output even with insufficient or less labeled data for histopathological image applications.
- To develop weakly supervised algorithms to perform tissue semantic segmentation from image level annotations.

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